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Chapter

# Perspective about Medicine Problems via Mathematical Game Theory: An Overview

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## Abstract

This chapter provides an overview of Game Theory with applications to medicine problems, including evolution of tumor cells and their competition, applications to neocortical epilepsy surgery and schizophrenic brain. Recent studies related to microarray games for cancer problems will be considered. These models may be used for applications to neurological and allergic diseases. At the end, the model of kidney exchange via the Matching Theory proposed by Alvin Roth, Nobel prize 2012, will be discussed.


**Keywords:** game theory, Nash equilibria, evolutionary stable strategy, tumor cells, thoracic surgery, neocortical epilepsy, kidney donation

## 1. Introduction

Mathematical Game Theory is a branch of Mathematics which analyzes strategic behaviors of decision makers which interact each other: the players. They have cooperation or competition each other. Game Theory started in 1944 with J.von Neumann and O.Morgenstein with the book which pick up their researches "Theory of Games and Economic Behavior". They started studying only zero sum games (intuitively if a player wins the other loses) and thanks to J.Nash, another giant in Games Theory, the general games (not necessary zero sum) were introduced and studied.

There are two great chapters in this science: cooperative games and noncooperative games. There is a "bridge" between cooperative and noncooperative games and it consists of the "repeated games". In fact if a game is repeated with infinite horizon the solution is in the cooperative zone (Folk Theorem) (see [1]).

In this contribution we consider medicine problems modeled by mathematical games. We present some models as evolution of cancer cells and their competition, applications to neocortical epilepsy surgery and schizophrenic brain. Some studies which we will see in details in the next sections with needed references, keep into account the microarray games which were studied to consider the cancer problem but applied also to neurological and allergic diseases. The model of kidney exchange is presented too, this is studied via an algorithm proposed by A.Roth, Nobel prize 2012. Also some management problems of modern health care are considered. Even if Game Theory is a young science, in many situations has revealed to be a fundamental tool as for the genetic analysis or to study images to determine cortical surface displacement during a surgery based on intraoperative stereo image information.

Furthermore studying the strategic interactions, this science permits us to investigate the relations between sick cells and healthy ones and among various genes.

We wish note that the examples are made with two or three players, for easy notations but they can generalize to a large number of players.

An interesting open problem is to apply the simulation techniques used in [2–5] and adapt them for simulations in medicine problems. Furthermore we can use the strategic method to evaluate behaviors for example in a military problem, and apply this model to evaluate the dangerous cells in a suspected disease.

This chapter is organized as follows: in Section 2 we analyze the Doctor Dilemma which is a generalization of the Prisoner Dilemma, in Section 3 we consider Evolutionary Game Theory, branch of Game Theory that can be successfully applied to Medicine models. In Section 4 we consider the evolution of cancer cells presenting many game models. In Section 5 we study the applications to brain models and in Section 6 we analyze the interesting problems of kidney exchange via the Matching Theory proposed by Alvin Roth, who won the Nobel Prize in 2012. Conclude the paper a rich but not exhaustive bibliography which invites to further reading of game theoretical texts.

## 2. Prisoner dilemma and doctor dilemma

We think that Game Theory offers to Medical Science a new interesting method to analyze and model some problems.

There are many papers about these two sciences studied together but for the complexity of the problem we can say that we are at the beginning of a new challenge team work.

Relieving pain and suffering is one of the most important doctors roles, so these have much gratification when they achieve this. Society is expecting that doctors successfully manage pain in fact this is one criterion that the Joint Commission certifies as health care organization in the United States. Given the relevance of trust and cooperation among patients and doctors for health care we can apply Game Theory to study the interaction in health settings and to understand the strategies which must be adopted to have the best payoffs for doctor and his/her patients [6].

In addition physician's compensation may depend on patients' satisfaction. But some problems might be: for example the patient could have no pain but he/she wants drugs for other motivations. How should the doctor do? This problem may be modeling as the Prisoner Dilemma where the players are the patient (player I) and the doctor (player II) and the strategies are respectively $X = \{real\ pain, fake\ pain\}$ and $Y = \{prescribe\ drugs, do\ not\ precibe\ drugs\}$.

This is the Doctor dilemma game where the best outcomes for both the players are not the equilibrium of the game.

| Doctor patient | Prescribe drugs | Do not prescribe drugs |
|---|---|---|
| Real pain | Patient satisfied,<br>High satisfaction score for the doctor,<br>Professionally rewarding | The patient dissatisfied,<br>Low satisfaction for the doctor |
| Fake pain | Patient satisfied,<br>High satisfaction for the doctor,<br>Even if it is professionally less rewarding | The patient dissatisfied,<br>Low satisfaction for the doctor,<br>Even if it is professionally most rewarding |

This game is similar, even if it is not symmetric, to the Prisoner Dilemma below.

| $I \backslash II$ | $L$ | $R$ |
|---|---|---|
| $T$ | 1, 1 | 5, 0 |
| $B$ | 0, 5 | 3, 3 |

In this game $X = \{T, B\}$ and $Y = \{L, R\}$ are the strategy spaces of player I and player II respectively. T is for Top, B is for Bottom, L is for Left and R is for Right, but these are only names.

The $NE$ is $(T, L)$ in fact.

$T = R_I(L)$ the best reply of player I to the strategy L of player II and.

$L = R_{II}(T)$ the best reply of player II to the strategy T of player I.

It is a nonefficient solution but in dominant strategies.

The situation is very complex: the physician cannot be sure if the patient tells true or not, the patient is in a position of vulnerability, the physician cannot guarantee the successful of his/her prescription (if any). The physician can fall prescribing drugs if they are not necessary or also necessary if these have collateral dangerous effects for the health patient. This wishes the drugs and if the doctor does not prescribe them, his/her trust falls down. There are a lot of problems in these decisions, some are discussed in [7].

Another interesting medicine problem is studied in [8], where the "consultation games" are introduced. The author considers important the cooperation between patients and doctors by building trust, obtaining information and solving problems. The physician payoffs depends on proposing care methods and communicating with patients. The payoff of patients depends sometimes from a fast provision of medical interview and sometimes from relationship with the doctor (in special way in case of chronic illness). Other patients wish a screening investigation but they do not know the possible harms involved. Also in these cases the games are useful to understand the best strategies.

In [9], the authors propose noncooperative games for surgery problems and cooperative games for the operating room settings to create a better synergy and improve the hospital efficiency and patients safety.

A reiterated process leads us to make a model via repeated games (see [10, 11] or through the combination of cooperative and not cooperative games. In real situations not all the players wish to cooperate: some of them cooperate but some else do not. In this case we speak about partially cooperative games, studied in [12].

## 3. Evolutionary game theory

A very interesting chapter is Evolutionary Game Theory proposed by Maynard Smith, a theoretical evolutionary biologist, geneticist and an aeronautical engineer to study mathematical models in biology and its strategic aspects.

Many socioeconomic and biological processes can be modeled with interacting individuals where players wish to maximize their own payoffs and in particular animals and genes maximize their individual fitness, [13, 14].

In evolutionistic selection, individuals wish to maximize the expected value of a measure of surviving otherwise they are substituted, to this goal they decide their strategies, not consciously but following evolution rules. The concept of human rationality is substituted by evaluative fitness, and Maynard Smith had many doubts on the first but no on the second.

We can apply this theory to understand the cancer cells propagation. In an evolutionary context we consider animals or bacteria players as maximizing their fitness so we consider steady state population dynamics. Intuitively each evolutionary player uses a strategy to maximize its payoff following the evolutionary theory and via a dynamical convergence to a stable outcome or the so called evolutionary stable strategy (*ESS* for short). An equilibrium deriving from an *ESS* is a refinement of a Nash equilibrium (*NE*) and it is a stable solution under small perturbations.

We will write the following example as a generalization of the well-known Hawk/Dove game.

In a human body there are 2 groups of cells: healthy cells and cancer cells, they want to "conquer" the human body and so they must fight. They can have a quiet behavior (D) or an aggressive behavior (H) and this is decisive to have the spreading of the disease or not. We call $c$ the cost of the fight and it depends from the resources body and the medicines given to the patient when the disease was discovered.

This game is written in the following matrix:

| $I \backslash II$ | $H$ | $D$ |
|---|---|---|
| $H$ | $1/2 - c,\ 1/2 - c$ | $1,\ 0$ |
| $D$ | $0,\ 1$ | $1/2,\ 1/2$ |

Player I and player II are animals in the original game (here we can think to two patients).

If both the animals have a pacific behavior, they divide the "prey", so their payoff is 1/2 (the individual is not completely ill).

If the behavior of a group of cells is $H$ and the other is$D$, the aggressive ones invade the human body and the other does not.

So the patient has the disease if the aggressiveness is from tumor cells instead he/she is recruited if it derives from healthy cells. If both the cells are aggressive, they obtain $1/2 - c$: they divide the human body but they have a detriment of strength (equal to cost $c$ for the fight).

Studying the *ESS* and the subsequent equilibria we can prove:

if $c \leq 1/2$ there is only one equilibrium from *ESS*: $(H, H)$.

if $c > 1/2$ there are no evolutionary equilibria from *ESS*.

This result is intuitive in fact if the fight cost is high (intuitively greater than 1/2) it is better do not fight and leave the prey (in our case the human body in its state).

This new theory may be applied to spatial stress variations, such as the case in cancer dynamics. In [10] the authors studied a game theoretical model in the dynamics of cooperators and cheater cells under metabolic stress hypotheses and spatial heterogeneity. Via Game Theory they tried to understand the dynamic of cancer tumor evolution under stress. They give a simulation of the development of cancer cells under the hypotheses of exchange of genetic material between the individuals (this process is called "horizontal gene transfer"). The authors suppose individuals can change their strategies from being cheaters to cooperators. A strategy can evolve by genetic evolution as a reply to the stress of the local environment. A combined dialog between these models and lab experiments can enrich our knowledge about tumor cells resistance.

To read further research about Evolutionary Game Theory and cancer, see [15–18].

Sometimes cancer cells in the primary tumor may stop growing (for example for restricted space or few oxygen) and some malignant cells may break away from the primary tumor. There are a lot of open questions: Which kind of tumor cells and how much go far from the primary tumor? Which of them migrate into the vessels? Which kind of circulating tumor cells and how many go in a second tumor? A games model which keeps into account the interactions among them and the environment, could be very useful. See [19].

## 4. Evolution of tumor cells

An unusual hypothesis about the cooperation of tumor cells may be found in [20]. The authors think tumor cells as players in a mathematical game, their interactions (intuitively their strategies even if not consciously decided), permit them to arrive to evolutionist fitness. Distinct tumor cells cooperate to overcome some host defenses by exchanging different products. Two nearby subclones can protect each other spending the process of tumorigenesis, thanks to malignant cells containing all nourishment for cancer growing.

Another model studying the cancer cells was introduced in [21] and generalized to multicriteria games (that is games with vector payoffs) in [22].

The authors consider, via mathematical game theory, the genic expression to investigate serious diseases as cancer. Their goal is to propose a method for evaluating the relevance of the genes as disease markers. The common application in Medicine is "to teach" a "classificator" to distinguish between healthy and sick subjects on the basis of samples given by doctors.

A method to make a feature selection is to use Cooperative Game Theory with transferable utility ($TU$-games in literature, see [10, 11].

Intuitively, each gene is considered in a coalition to which a value is assigned and it shows how much these genes expressions suggest to distinguish between healthy and sick subjects. In the cited paper, the authors applied mathematical Game Theory to analyze the results obtained with microarray techniques which allow to make a photo of thousand of genes expressions through a unique experiment. The starting point is studying the genetic expression in a cell sample and verifying some particular biological conditions (for example the cells of a subject affected by a tumoral disease). Studying the "microarray games" we can evaluate the relevance of genes to regulate or to provoke the onset of a pathology taking into account the genes interactions each other.

In this context the Shapley and the Banzhaf values (see [10, 11] are studied as a measure about the "importance" of a gene ("relevance index") in the diagnosis.

The authors in [22] study the vector Shapley value for microarray multiobjective games basing on the idea of "partnership of genes" (as in [21]). Intuitively this is a genes' group with correlated characterizations and which is very useful to study if the disease is developing.

The experimental results have shown that the Shapley value is a valid tool to evaluate the expressions of genes and to predict a tumor disease.

The advantage of considering a coalitional game is the possibility to compute a numerical index, the so called *relevance index* which intuitively represents the relevance of each gene taking into account the relevance of the others when, for example, a tumor disease is growing.

In general is important to consider multiobjective games (or vectorial games) instead of scalar ones, because the players have not one but more objective "to maximize" and often these goals are not comparable. In a medicine problems there are many parameters "to optimize" so it is important to keep into account them together, the solution will be more precise and it will allow us to better understand the presence of a disease.

About multiobjective games and their solutions you can see: [12, 23–25].

In the following example we consider two real expression matrices where the first $M^{S_R}$ contains the samples of patients without considered disease, the second $M^{S_D}$ contains samples of patients who have some disease signals, so we must investigate about two medical parameters in the set of genes $\{1, 2, 3\}$ which are considered the players in our model. The study is made w.r.t. the samples $\{a, b, c, d\}$ in the case of patients without disease and w.r.t. the samples $\{a, b, c\}$ in the case of patients with disease signals. After a comparison between the two matrices $M^{S_R}$ and $M^{S_D}$ written below, we arrive to write the microarray cooperative game for our model.

The two objectives may be for example the values of protein index and glycemic index. If we will study more objectives (suggested by the doctors), our model will be more precise.

$M^{S_R}$

| | **Sample a** | **Sample b** | **Sample c** | **Sample d** |
|---|---|---|---|---|
| Gene 1 | $\begin{pmatrix} 7.77 \\ 0.5 \end{pmatrix}$ | $\begin{pmatrix} 8.95 \\ 0.2 \end{pmatrix}$ | $\begin{pmatrix} 6.48 \\ 0.3 \end{pmatrix}$ | $\begin{pmatrix} 1.94 \\ 0.6 \end{pmatrix}$ |
| Gene 2 | $\begin{pmatrix} 20,40 \\ 12 \end{pmatrix}$ | $\begin{pmatrix} 14,75 \\ 10 \end{pmatrix}$ | $\begin{pmatrix} 34.88 \\ 4 \end{pmatrix}$ | $\begin{pmatrix} 20.35 \\ 5 \end{pmatrix}$ |
| Gene 3 | $\begin{pmatrix} 0.49 \\ 8 \end{pmatrix}$ | $\begin{pmatrix} 5.79 \\ 13 \end{pmatrix}$ | $\begin{pmatrix} 1.00 \\ 20 \end{pmatrix}$ | $\begin{pmatrix} 16.47 \\ 9 \end{pmatrix}$ |

$M^{S_D}$

| | **Sample a** | **Sample b** | **Sample c** |
|---|---|---|---|
| Gene 1 | $\begin{pmatrix} 3.26 \\ 0.9 \end{pmatrix}$ | $\begin{pmatrix} 1.63 \\ 0.4 \end{pmatrix}$ | $\begin{pmatrix} 1.58 \\ 0.7 \end{pmatrix}$ |
| Gene 2 | $\begin{pmatrix} 89.52 \\ 4.6 \end{pmatrix}$ | $\begin{pmatrix} 17.35 \\ 11 \end{pmatrix}$ | $\begin{pmatrix} 15.76 \\ 18 \end{pmatrix}$ |
| Gene 3 | $\begin{pmatrix} 4.66 \\ 11 \end{pmatrix}$ | $\begin{pmatrix} 0.3 \\ 3321 \end{pmatrix}$ | $\begin{pmatrix} 19.44 \\ 12 \end{pmatrix}$ |

From these two tables we can build a cooperative microarray game (with two objectives) which is:

| $S$ | $\varnothing$ | {1} | {2} | {3} | {1,2} | {1,3} | {2,3} | {1,2,3} |
|---|---|---|---|---|---|---|---|---|
| $v(S)$ | 0<br>0 | 0<br>$\frac{1}{3}$ | $\frac{1}{3}$<br>0 | 0<br>$\frac{1}{3}$ | $\frac{1}{3}$<br>$\frac{2}{3}$ | $\frac{2}{3}$<br>$\frac{2}{3}$ | $\frac{1}{3}$<br>$\frac{1}{3}$ | 1<br>1 |

So the physician problem studied through microarrays analysis may be translated into a cooperative game and studied with the usual tools of the theory (for more and not easy details see [22]). Here the authors consider the vector Shapley value and the Banzhaf one as the genes relevance indices or disease markers but a research is in progress about other solutions perhaps more suitable and a comparison among the results.

## 5. Game theory and brain

In some papers of Game Theory diseases connected with our brain are considered, also microarray games may be applied to study neurological diseases, see [26].

In the paper [27], the author consider Game Theory in relation to schizophrenic brain. The idea was emerging from the disease of John Nash. He won the Nobel prize in 1994 for his fundamental works about the concept of equilibrium (the so called Nash equilibrium), the existence of at least one equilibrium in mixed strategies in finite games and the existence of an equilibrium in bargaining games [10, 11].

The disease of John Nash was discovered when he was 29 years old and a brilliant mathematics researcher. He generalized the games from a zero sum (introduced by von Neumann and Morgestein) to general games. This is very important, because in the real life only a few games are zero sum that is a player wins and the other loses, but everyone wins something.

The author applies the theory of strategic interaction to understand the behavior of schizophrenic brain, suggesting us the study between the limbic system and the cerebral hemispheres and between the two cerebral hemispheres. We have an equilibrium when the brain is optimally working, that is when an hemisphere is not prevalent on the other but they are in equilibrium. In our model of a noncooperative game the two cerebral hemispheres are seen as two players playing against each other. This is possible because, as schizophrenic brain researcher teaches us, the two hemispheres are isolated one from other or because there is too much connection between them. In any case the effect is disastrous. Also the relations between the lower brain functions may be seen in the same way. Following the research about schizophrenic disease one hemisphere does not interfere with the optimal functioning of the other.

In the Prisoner Dilemma the two players decide contemporary and independently their strategies that is no one knows what the other does, so it may be a good model for a schizophrenic brain and to understand better this terrible disease.

Games are used also for applications to neocortical epilepsy surgery, see [28] where this topic is applied to cortical surface tracking during the neurosurgery to have information about the brain surface deformation and to have a good image. This method has a high percent of success. Surprisingly this young science is applied also to the image analysis, [29, 30] and to estimate the brain deformation.

Deformations are studied as strategies in a noncooperative game.

The goal is the research of a *NE* which is a strategy profile where there is no incentive for players to deviate unilaterally from their strategy.

In the surgery game we consider two hypothetical players whose strategies are respectively the dense displacement field and the camera calibration parameters which are used to transform points from the 3D intraoperative field into stereo image space. The utility functions are the opposite of the cost functions corresponding to the values for the operations.

All this can be formulated as a noncooperative game in fact changing the values of the camera calibration parameters, also the search of displacement field may vary. The authors use a game theoretic algorithm based on a Bayesian approach to have information about the cortical surface deformation.

A paper about neuroscience is [31] where combining the modern neuroscience methods and mathematical games, a neuroeconomics approach, studying the knowledge of brain mechanism, helps us in keeping social decisions.

## 6. The matching theory and kidney exchanges

Sometimes, many scientific discoveries are not easy to support economically or awake bioethics problems so these may not be easily applied to disease patients. This problem happens, for example, in the kidney exchanges. In this exchange the successful has arrived to $95 - 97\%$ and the sensibility of giving a transplant organ after death has grown. In despite to these great successful there are many patients waiting an organ transplant because there are not a sufficient number of organs to give to needing patients.

In the sub Saharan Africa, each years a lot of people (more than 5 million) die because they have no admission neither to hemodialysis nor kidney transplant. There is another great problem, which is incompatibility between donors and recipients. In the most number of countries the unique admissible solution by law is the existence a family degree between donor and recipient. Sometimes donor and recipient are not compatible because their blood group or other characteristics of their immune system.

In 2012 Alvin Roth, professor at the Stanford University, won the Nobel prize for his Matching Theory which started from a kidney exchange problem [32, 33]. To explain intuitively this theory we make a simple example: let us suppose that a father needs a kidney transplant, because in a few week he risks to die, and her daughter wishes to give it to him but she is not compatible. In the world there is certainly another pair in the same situation. So the Matching Theory suggests to create a special chain among people who wants give a kidney to a dear person but because incompatibility this is not possible. Starting from Matching Theory a great project presented by Alvin Roth and other scientists, the Global Kidney Exchange Program, this is an international system with donors and recipients with compatible organs. An algorithm proposed by Roth, tests the pair in the program and finds the best match between waiting patients and donors so the patients may find a compatible organ in time for their survival. This program is very important not only because it gives a good life to a person but also for the economic tolerability of the sanitarian system. One objective is to help people needing kidney exchange in the poor countries (where there is no hemodialysis). If a kidney for an Italian patient comes from an African patient, this will have a new kidney and he will live and our Italian patient will have a better life with less cost for the National Sanitarian Service. Keeping into account the compatibility between pair of donors and receivers, the problem may be in great part resolved. Making the mathematical model via a game, we can prove that the *NE* is efficient because all players obtain the best.

As you can imagine there are some ethical problems to consider in fact in an international chain some unscrupulously people could enter and the problem of organ traffic must be supervised. The Global Kidney Exchange has had the endorsement of the American Society of Transplant Surgeons and the World Health Organization has promoted this challenge idea.

(See https://www.profignaziomarino.com/mc/468/trapianti-d-organo-la-proposta-rivoluzionaria-di-un-nobel). About kidney exchange and Game Theory see also [34] and references in it.

## 7. Conclusion

The overlapping results obtained on mathematical games and those in medical literature may not be casual, medicine models studying the disease onset could make use of methods of this young science. Once again we understand that scientific research need of a studious team in many science branches: mathematicians, engineers, medicine, biologists, economists and so on.

Mathematical games contribute to suggest us the ways to verify new ideas and they permit us to prove with precise calculations the logic of our reasoning because the better understanding of these diseases is an important step.

We remark that for all notions which we have not defined in the text, we refer to already cited [10, 11, 13, 35] the book of Roger Myerson, Nobel Prize 2007 for the theory of Mechanism Design.

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